The novel γ9δ2 T-cell activator ICT01 combined with azacitidine-venetoclax shows high rates of complete remission in older/unfit adults with newly diagnosed acute myeloid leukemia: interim results from Phase 1 study EVICTION

Poster # 2876

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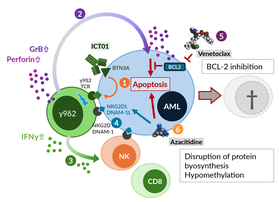
BACKGROUND

- ICT01 is a novel, first-in-class humanized anti-butyrophilin 3A (BTN3A) monoclonal antibody that selectively activates γ9δ2 T cells, leading to both direct cytotoxicity against AML blasts and indirect immune modulation through activation of CD8 T and NK cells, collectively mounting a synergistic anti-leukemia response (Figure 1).
- In preclinical studies, ICT01-mediated γ9δ2 T-cell activation protected both γ9δ2 T and NK cells against venetoclax-induced cell death.
- Preclinical studies demonstrated that co-administration of ICT01 and azacitidine-venetoclax significantly increased the blast killing capacity. In a xenograft mouse model with adoptive γ9δ2 T cell transfer, ICT01 in combination with azacitidine-venetoclax significantly delayed tumor growth and improved median survival of animals compared to either treatment alone (Figure 2).
- Previously, we reported that increasing doses of up to 75 mg ICT01 Q3W as monotherapy for the treatment of R/R AML was well-tolerated without any dose-limiting toxicities (Garciaz et al. Ann Oncol 2023; 34(suppl 2): abstr #543).
- Together with favorable PK and supportive PD data indicating consistent and effective γ9δ2 T-cell activation, these data supported further investigations of ICT01 in combination with azacitidine-venetoclax in newly diagnosed patients with AML.

Figure 1: Azacitidine-venetoclax sensitize AML blasts mounting a synergistic ICT01-mediated anti-leukemic effect through activated γ9δ2 T, NK and CD8 cells

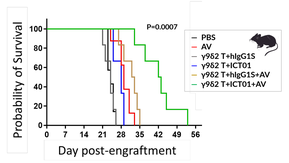


1. ICT01 switches BTN3A receptor conformation from 'inactive' to 'active' ⇨ 'active' BTN3A of AML blasts directly engages with γ9δ2 T-cell receptor
2. ⇨ leading to direct killing via GrB/perforin pathway[1,2]
3. ICT01-activated γ9δ2 T cells activate granulocytes and NK cells[3]
4. Co-stimulatory factors (NKG2D, DNAM-1, ICAM1) enhance γ9δ2 T-cell functions[3,4]
5. Venetoclax overcomes GrB/perforin resistance of AML blasts and enhances the anti-leukemic efficacy of γ9δ2, NK and CD8 T cells[5–7]
6. Azacitidine improves immune-effector–cell recognition of AML blasts through NKG2DL (secondary stress ligand) induction and dsDNA accumulation.[7–9]

References: **1.** De Gassart et al. *Sci Transl Med* (2021) | **2.** Kabelitz et al. *Cell Mol Immunol* (2020) | **3.** ImCheck, data on file, (2023) | **4.** Siva-Santos et al. *Nat Rev Cancer* (2019) | **5.** Sutton et al. *Cell Death Dis.* (2012) | **6.** Lickliter et al. Br J Cancer (2007) | **7.** Lee et al. *Blood* (2021) | **8.** Wu et al. *Int Immunopharmacol* (2023) | **9.** Gang et al. *BCJ* (2014)

Abbreviations: GrB, granzyme B; IFNγ, interferon γ; NKG2D(L), natural killer group 2 member D (ligand).

Figure 2: ICT01 plus azacitidine-venetoclax synergistically increases the anti-leukemic activity *in vivo*



NSG mice engrafted with human AML cell line (**MOLM14**) and treated with **azacitidine** (2mg/kg/day IP for 5 days/week for 1 week), **venetoclax** (40mg/kg/day PO for 5 days/week for 3 weeks), adoptive transfer of human **γ9δ2 T cells** (3×10^6 cells QW IV for 4 weeks), and **ICT01** or **hIgG1** (1mg/kg BIW IV for 4 weeks); P-value (γδT+ICT01+AV vs. AV) calculated with log-rank (Mantel-Cox) test.

Abbreviations: AV, azacitidine+venetoclax; hIgG1S, control antibody; MOLM14, AML cell line; NSG, NOD Scid Gamma mouse.

STUDY METHOD AND DESIGN

Main eligibility criteria
- Adults with newly diagnosed AML ≥ 75 years old or unfit to receive induction chemotherapy due to comorbidities;
- No t(15;17), t(8;21), inv(16), or t(16;16) karyotypic abnormality;
- No history of myeloproliferative neoplasm including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukemia with or without BCR-ABL1 translocation, or AML with BCR-ABL1 translocation.

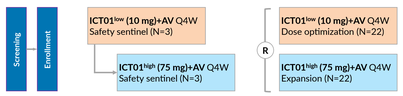
Efficacy assessments (ELN 2022 criteria)
- CR rate, proportion of patients with complete remission (CR)
- CRc rate, proportion of patients with CR with full, partial (CRh) or incomplete (CRi) hematological recovery
- Efficacy-evaluable (EE) population

Safety
- Treatment-emergent adverse events (TEAE)

Biomarkers
- BTN3A expression on AML blasts in bone marrow (BM)
- Number and activation of γ9δ2 T cells in blood and BM

Figure 3: Study design

1L AML patients older/unfit for induction chemotherapy treated with ICT01-azacitidine-venetoclax



Abbreviations:
A, azacitidine 75 mg/m² on D1–7 Q4W IV or SC; D, day;
V, venetoclax given at 100 mg / 200 mg / 400 mg on D1/2/3 of Cycle 1 and then 400 mg QD Q4W.

Table 1: Patient demographics

Variables	Safety population ICT01low+AV (N=18)	ICT01high+AV (N=15)	Pooled (N=33)
Age [median (range)]	**75 (70-87)**	**75 (64-84)**	**75 (64-87)**
≥ 75	10 (56)	9 (60)	19 (58)
ECOG performance status [n(%)]			
2 or 3	3 (17)	5 (33)	10 (33)
AML type [n(%)]			
Secondary	1 (6)	3 (20)	4 (12)
AML-MR	9 (50)	6 (40)	15 (45)
Bone marrow blasts [median% (range)]	**33 (7-95)**	**26 (9-82)**	**26 (5-95)**
< 30 %	9 (50)	8 (53)	17 (52)
≥ 30-50%	5 (28)	2 (13)	7 (21)
≥ 50%	4 (22)	5 (33)	9 (27)
History of cytopenia	10 (55)	5 (33)	15 (45)
Mutations [n(%)]			
NPM1	1 (6)	3 (20)	4 (12)
IDH1/IDH2	4 (22)	—	4 (12)
FLT3-ITD (orTDK)	1 (6)	—	1 (3)
TP53	4 (22)	7 (47)	11 (33)
Secondary-type mutations	5 (28)	1 (7)	6 (18)
Other/NOS	4 (22)	5 (33)	9 (27)
Cytogenetic Risk			
Intermediate	15 (83)	10 (67)	25 (76)
Poor	3 (17)	5 (33)	8 (24)
Molecular Prognostic Risk Signature (mPRS) [n(%)]			
Favorable	13 (72)	8 (53)	21 (64)
Intermediate (*N/K RAS, FLT3-ITD*)	1 (6)	—	1 (3)
Adverse (*TP53*)	4 (22)	7 (47)	11 (33)

SAFETY OF ICT01 + AZACITIDINE-VENETOCLAX

Table 2: Safety summary

TEAE category [n (%)]	ICT01low+AV (N=18)	ICT01high+AV (N=15)
Patients with any TEAE	**18 (100)**	**15 (100)**
Maximum CTCAE Grade 1	1 (6)	1 (7)
Maximum CTCAE Grade 2	0	2 (13)
Maximum CTCAE Grade 3	8 (44)	4 (27)
Maximum CTCAE Grade 4	8 (44)	6 (40)
Maximum CTCAE Grade 5	1 (6)	2 (13)
Patients with any ICT01-related* TEAE	**9 (50)**	**4 (27)**
Maximum CTCAE Grade ≥ 3	3 (17)	2 (13)
Patients with any SAE	**12 (67)**	**8 (53)**
Patients with any ICT01-related SAE	2 (11)	2 (13)
Patients with any TEAE leading to permanent study discontinuation	**1 (6)**	**1 (7)**
Patients with any ICT01-related TEAE leading to permanent study discontinuation	0	0
Patients with any TEAE leading to treatment interruption and/or dose reduction	**3 (17)**	**1 (7)**
Patients with any ICT01-related TEAE leading to treatment interruption and/or dose reduction	0	0
Patients with any TEAE leading to death	**1 (6)**	**2 (13)**
Patients with any ICT01-related TEAE leading to death	0	0

EFFICACY OF ICT01-AZACITIDINE-VENETOCLAX

Table 3: Summary of efficacy

Variables	ICT01low+AV (N=10)	ICT01high+AV (N=10)	Pooled (N=20)
Response			
CRc (95% CI)	**10** 100% (69-100)	**8** 80% (44-97)	**18** **90%** (68-99)
CR (95% CI)	**6** 60% (26-88)	**4** 40% (12-74)	**10** **50%** (27-73)
CRc_{MRD-}	4/5 (80%)	2/7 (29%)	6/12 (50%)
Time to first CRc response [months, median (range)]	1.4 (0.7–2.4)	1.4 (0.7–3.0)	1.4 (0.7–3.0)
Mortality			
30-day mortality [n(%)]	**0**	**0**	**0**

Figure 5: CR & CRc rates by treatment cycle

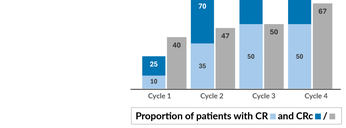


Table 4: Efficacy across prognostic molecular subtypes

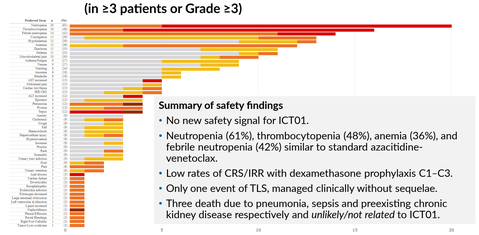
Variables		Evaluable patients Total (N=20) [N (%)]	CR (N=10) [n/N (%)]	CRc (N=18) [n/N (%)]
Mutations [n/N(%)]	Prognosis[†]			
NPM1	favorable	4 (20)	**3 (75)**	**3 (75)**
IDH1/IDH2	intermediate	4 (20)	**2 (50)**	**4 (100)**
FLT3-ITD	intermediate	0	**0**	**0**
TP53	poor	5 (25)	**2 (40)**	**4 (80)**
*AML, secondary-type**	poor	5 (25)	**1 (20)**	**4 (80)**
Other/NOS	favorable	4 (20)	**2 (50)**	**4 (100)**
mPRS [n(%)]				
Favorable		15 (75)	**8 (53)**	**14 (93)**
Intermediate		0	**0**	**0**
Adverse		5 (25)	**2 (40)**	**4 (80)**

*Secondary-type AML (poor prognosis) mutations are SRSF2, SF3B1, U2AF1, ZRSR2, EZG2, BCOR, STAG2, ASXL1

References: [†]Döhner et al. Blood 2024; doi:10.1182/blood.2024025409 | [‡]DiNardo et al. NEJM 2020;383:617-629 | [†]Pratz et al. Am J Hematol. 2024;99:615–624 | [‡]Othman et al. Blood Adv. 2024;1(3):100017.

Abbreviations: AV, azacitidine-venetoclax combination treatment; CRc, composite complete response (CR+CRh+CRi); CRh, CR with partial hematological recovery; CRi, CR with incomplete hematological recovery; ICT01^{low}/^{high}, ICT01 10 mg/75 mg Q4W; mPRS, molecular prognostic risk signature; NOS, not otherwise specified; NR, not reported.

Figure 4: Treatment-emergent adverse events (in ≥3 patients or Grade ≥3)

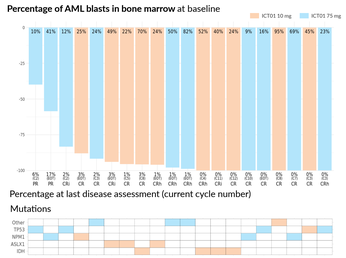


Summary of safety findings
- No new safety signal for ICT01.
- Neutropenia (61%), thrombocytopenia (48%), anemia (36%), and febrile neutropenia (42%) similar to standard azacitidine-venetoclax.
- Low rates of CRS/IRR with dexamethasone prophylaxis C1–C3.
- Only one event of TLS, managed clinically without sequelae.
- Three death due to pneumonia, sepsis and preexisting chronic kidney disease respectively and *unlikely/not related* to ICT01.

CTCAE categories: Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5.

Abbreviations: C, cycle; CRS, cytokine release syndrome; IRR, infusion-related reaction; TLS, tumor lysis syndrome.

Figure 6: Greatest percent decrease in blasts from baseline



Abbreviations: C, Cycle; CK, complex karyotype; FU, follow-up; NOS, not otherwise specified; NR, no response.

Figure 7: Best overall response and treatment duration

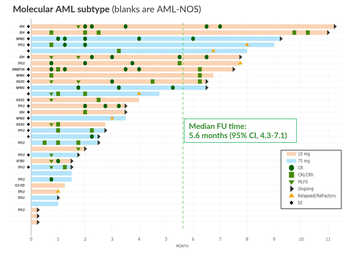
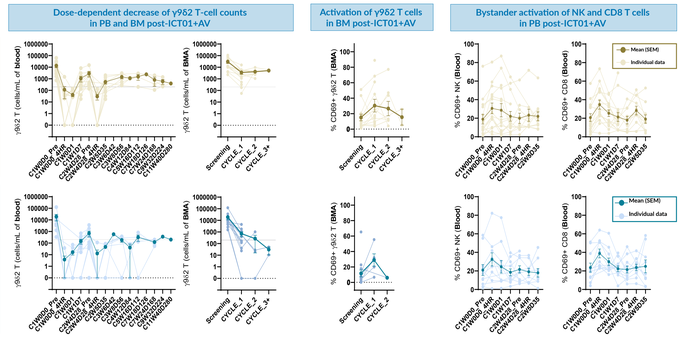


Figure 8: ICT01 activates γ9δ2 T cells and triggers a downstream immune response



Abbreviations: AV, azacitidine+venetoclax; BM, bone marrow; BMA, bone marrow aspirate; C, cycle; D, day; PB, peripheral blood; W, week.

In this ongoing Phase 1 study in newly diagnosed patients with AML older/unfit for induction chemotherapy, both ICT01^{low} and ICT01^{high} were safe and very well tolerated, and generated high rates of CR and CR/CRi.

- ICT01 in combination with azacitidine-venetoclax has a manageable safety profile. No 30-day mortality, no Grade 5 drug-related adverse events and no dose-limiting toxicity were reported. Most common Grade 3 or 4 adverse events were neutropenia, febrile neutropenia, and thrombocytopenia.
- ICT01 in combination with azacitidine-venetoclax demonstrates high efficacy in 1L older/unfit patients newly diagnosed with AML across different molecular subtypes.
- ICT01 resulted in rapid γ9δ2 T-cell activation, which was transient for ICT01^{low} and sustained for ICT01^{high}.

SCAN ME

Study sponsored by ImCheck Therapeutics